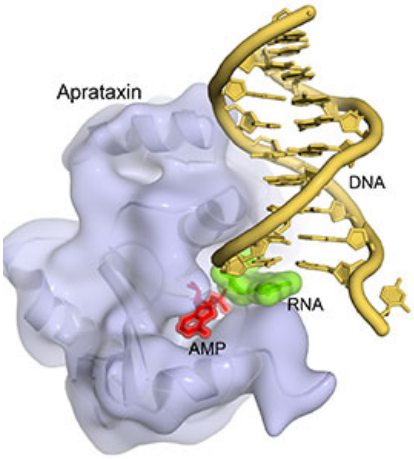
NIEHS study identifies protein involved in DNA damage removal

By Robin Arnette

For years, scientists thought that the majority of DNA damage occurred as a result of radiation, toxicant exposures, or some other environmental insult, but NIEHS research has determined that the insertion of RNA into DNA may be an underappreciated source of many more unknown lesions. In the genetic arms race, organisms from yeast to humans have a protein weapon called aprataxin that counters the RNA-triggered onslaught.

The team, led by Scott Williams, Ph.D., head of the NIEHS Genome Stability Structural Biology Group, published the results online Dec. 22 in Nature. The scientists used X-ray crystallography to visualize how human aprataxin handles RNA-DNA damage, and are the first to identify an enzyme removing a lesion arising from RNA-DNA. They call this process the RNA-DNA damage response, and its discovery may help uncover some of the genetic mishaps that contribute to neurodegenerative diseases, as well as lead to potential new therapies for cancer patients.



The molecular structure depicts how human aprataxin processes an RNA-DNA lesion. Aprataxin (blue) binds to the lesion (red) that results from the insertion of RNA (green) into DNA (yellow). (Photo courtesy of Scott Williams)

Targeting RNA

Scott Williams said RNA incorporation into DNA happens by accident during replication and has largely unknown consequences. He explained why removing RNA from DNA was so important.

"When you have RNA in place of DNA, DNA ligase, the enzyme that seals DNA ends, stops part way through its reaction," he said. "Rather than protecting the genome, it leaves a lesion that makes the damage worse."

Scott Williams reiterated that RNA-triggered lesions were a new idea in the field of DNA repair. (Photo courtesy of Steve McCaw)

The lesions prevent the DNA from making copies of itself, so the cell has to address the injury. As one of the proteins involved in DNA repair pathways, aprataxin spots these RNA-DNA lesions and removes them. However, mutations in the human aprataxin protein affect its ability to bind and eliminate RNA-DNA damage, and result in a rare, heritable cerebellar-wasting disease known as ataxia with aculomotor apraxia 1, as well as other disorders, including multiple system atrophy, a Parkinson's-like condition.

This study also furthers the work done by Thomas Kunkel, Ph.D., head of the NIEHS DNA Replication Fidelity Group, and research fellow Jessica Williams, Ph.D., who are co-authors on the paper. Kunkel and Jessica Williams study DNA polymerases, the enzymes that replicate DNA and also incorrectly insert RNA into DNA. RNA incorporation is a major cause of genetic instability and actually happens quite frequently.

"Current estimates for the number of ribonucleotides incorporated per round of DNA synthesis are 13,000 for yeast and greater than 1,000,000 for a mammalian cell," said Jessica Williams. "This number exceeds the total of all other DNA lesions studied in the DNA repair field and provides an enormous potential to create toxic lesions that require aprataxin for repair."

Designing cancer therapies

This recent aprataxin work brings scientists closer to figuring out causes of neurodegenerative disease, but may also benefit cancer patients. Percy Tumbale, Ph.D., an NIEHS Intramural Research Training Award fellow in Scott Williams' group and co-first author on the paper, said that, under the right circumstances, blocking aprataxin function might cause cancer cell death.

"We are exploring the possibility that we can use aprataxin's atomic structure to develop inhibitors of this enzyme," Tumbale said. "When combined with agents that create DNA damage or block other DNA damage response pathways, aprataxin inhibitors may have utility in cancer therapy."

Citation: Tumbale P, Williams JS, Schellenberg MJ, Kunkel TA, Williams RS. *(http://www.nature.com/nature/journal/vaop/ncurrent/full/nature12824.html)*

2013. Aprataxin resolves adenylated RNA-DNA junctions to maintain genome integrity. Nature; doi: 10.1038/nature12824 [Online 22 December 2013].

Thanks to Tumbale's expertise in X-ray crystallography, the Scott Williams group was able to crystallize mutant forms of aprataxin engaged with RNA-DNA lesions. (Photo courtesy of Steve McCaw)

Jessica Williams' work with DNA polymerase epsilon was essential to the research. (Photo courtesy of Steve McCaw)

Matthew Schellenberg, Ph.D., is a visiting fellow in the Scott Williams group. He, Tumbale, and Jessica Williams share first authorship of the article. (Photo courtesy of Steve McCaw)

Kunkel is a leading authority on DNA replication fidelity. About five years ago, his group found that RNA is transiently incorporated into human genomes and removed. (Photo courtesy of Steve McCaw)

The Environmental Factor is produced monthly by the National Institute of Environmental Health Sciences (NIEHS) *(http://www.niehs.nih.gov/)*
, Office of Communications and Public Liaison. We welcome your comments and suggestions. *(bruskec@niehs.nih.gov)*